

# Manuscript Details

<b>Manuscript number</b>	JVC_2017_24
<b>Title</b>	European Society of Veterinary Cardiology (ESVC) Screening Guidelines for Dilated Cardiomyopathy in Doberman Pinschers
<b>Article type</b>	Invited review article

## Abstract

Background: Dilated cardiomyopathy (DCM) is the most common cardiac disease in large breed dogs and is inherited in Doberman Pinschers with a high prevalence (58%). Objective: the European society for veterinary cardiology (ESVC) convened a task force to formulate screening guidelines for DCM in Doberman Pinschers. Recommendations: screening for occult DCM in Dobermans should start at three years of age and use both Holter monitoring and echocardiography. Yearly screening over the life of the dog is recommended, as a one-time screening is not sufficient to rule out future development of DCM. The preferred echocardiographic method is the measurement of the left ventricular volume by Simpson Method of disc (SMOD). Less than 50 single VPCs in 24 hours is considered to be normal in Dobermans, although detection of any number of VPC is cause for concern. Greater than 300 VPCs in 24 hours, or two subsequent recordings within a year showing between 50 to 300 VPCs in 24 hours is considered diagnostic of occult DCM in Doberman Pinschers regardless of the concurrent echocardiographic findings. The guidelines provide also recommendations concerning ancilliary tests, that are not included in the standard screening protocol, but may have some utility when recommended tests are not available or financially untenable on an annual basis. These tests include biomarkers (cTNI and NT-proBNP) as well as short-time ECG recordings. Conclusion: the current guidelines should help to establish an early diagnosis of DCM in Doberman Pinschers.

<b>Keywords</b>	DCM;cTNI;NT-proBNP;Simpson Method of disc;24-hours-ECG
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## Submission Files Included in this PDF

### File Name [File Type]

Cover letter.docx [Cover Letter]

Response to the reviewers R1- final.docx [Revision Notes]

ESVC Screening Guidelines for DCM in Doberman Pinschers R2-final-edited.docx [Manuscript]

Figure1 final.tif [Figure]

Figure 2.tif [Figure]

FIGURE 3.jpg [Figure]

FIGURE 4.tif [Figure]

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Response to the reviewers from the authors:

We would like to thank the reviewers for their greatly appreciated review and their time and constructive criticism of our manuscript.

We have included all recommendations – and have only one suggestion from reviewer 2 left open for the decision by the editor.

We apologize for the many spelling mistakes and grammatical errors and made sure that in the current version, all errors were eradicated.

-Reviewer 1:

Overall, this is a useful set of guidelines to help vets to reach a correct diagnosis of DCM in the Doberman. The authors have done a thorough job of assimilating all the relevant clinical research on the topic. The images used to illustrate the guidelines are clear and of high quality.

It is disappointing that there are several spelling mistakes, some omitted words and grammatical errors, as well as frequent misuse of punctuation throughout the manuscript. At times, this misuse of punctuation significantly interferes with the clarity of the statement being made e.g. Line 275 - 278. "Comment: Although the diagnosis of DCM can be established, if only one parameter is above the reference values, the accuracy of diagnosis improves, if both, diastolic and systolic measurements are above the cut-off values."

Two of the authors have English as a first language so there is no reason for this. A careful and thorough read-through of the manuscript should have been done by all authors prior to submission.

Lines 73-75. The statement "Ventricular premature complexes (VPCs) are a common finding in the occult phase of the disease, and about 30% of affected dogs die suddenly before the onset of congestive heart failure." needs referencing.

→ added references

Lines 78-87. This section dealing with effect of gender is confusing and some statements seem contradictory. Please reword to improve flow and clarity for reader.

→ amended

Lines 89-91. "Female dogs seem to have a slower progressive disease with VPCs detected with a 24h (Holter) as the only abnormality found, even in the older female dogs." The word ECG is missing after 24h. Rather than "slower progressive disease", it would be more correct to say "a slowly progressive form of the disease" or "slower disease progression". Are the authors saying that these female dogs never go on to

develop echo changes (i.e. they just have an arrhythmogenic form of the disease) or that the echo changes just develop later in females than in the males? Please clarify what is meant by this statement for the reader.

→ the paragraph was rewritten for clarification.

## -Reviewer 2

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This is an interesting, timely and authoritative review, which is certainly appropriate for publication in JVC. However, I feel that there are some areas which would benefit from clarification and/or additional explanation and references, as detailed below, and I would be grateful if you would consider these as I think they would be of benefit to the reader. There are also many linguistic amendments/corrections required, as listed below:

### CLARIFICATIONS / MODIFICATIONS:

- Line 1: Should the title perhaps be "... (ESVC) **Proposed** Screening Guidelines for ..."?  
→ we leave this comment to the editor for decision. As the ESVC formed a committee and approved the guidelines, we feel that they are not only proposed, but approved and therefore we feel that "proposed" is not necessary
- **Introduction** (line 66 onwards): In an authoritative review such as this, I feel it would be appropriate to define "dilated cardiomyopathy", with an appropriate reference(s), and similarly to define what you mean by the "occult phase" in this breed and to discuss how long how long the occult phase might last in this breed and how quickly it progresses, how variable this is (in addition to your discussion of the male/female differences in presentation)?  
→ amended. We added more information to the introduction, i.e. definitions and also more about the occult phase of the disease.
- Line 70: It is arguable whether idiopathic DCM occurs in the Boxer breed, although there is probably some geographical variation in this. Most cases of a DCM phenotype in Boxers are probably an end-stage of arrhythmogenic cardiomyopathy. Therefore I feel it might be better to omit the Boxer breed from this list.  
→ Boxer removed
- Lines 72-75: Can you provided a reference or references to back-up these statements, please?  
→ done
- Lines 100-101: "... in combination with the known rate of progression ..." - can you expand on this please (see comment above under "Introduction")?  
→ done
- Lines 118-119, **Screening Frequency**: This first sentence repeats what was said in the previous paragraph, and can probably be omitted?  
→ sentence removed
- Lines 148-170, **Comments on special situations**: It might be appropriate here to discuss the day-to-day variability of arrhythmia occurrence and frequency and to cite previous publications on this (even if these looked at other breeds)?  
→ done
- Line 176: "*Basic guidelines*" - can you clarify and/or insert a reference here please?  
→ added references
- Line 185: Reference [20] seems to be the same as reference [6]?  
→ changed and made into one
- Lines 298-300, **also** lines 685-686: Although commonly used (especially for HOCM in cats), "anterior" is **not** an approved term in veterinary anatomical nomenclature, and I feel that this journal, and an authoritative review such as this, should use **only** approved veterinary anatomical nomenclature? Therefore I would suggest **replacing** "anterior mitral valve leaflet" with "**septal** mitral valve leaflet" and **replacing** "anterior motion" with "motion



towards the interventricular septum", e.g. in lines 299-300 **and** 685-686: "maximal motion (E-point) of the septal mitral valve leaflet towards the interventricular septum"?

→ amended

- Lines 443 **and** 461: I assume "1 VPC" should be "1 VPC/5 minutes"?

→ changed to 1 VPC/5 minutes

#### LINGUISTIC / TYPOGRAPHICAL AMENDMENTS:

**All corrections/suggestions have been done – thank you again for the thorough review!**

- Lines 30, 35 (in Abbreviation Table), 51 **and** 490: Please **replace** "Simpson Method of disc" *with* "Simpson's method of discs" in all 4 occurrences
- Line 35 (in Abbreviation Table): cTnI is usually taken to mean **cardiac** troponin I, not *circulating* troponin I?
- Line 35 (in Abbreviation Table): VPC: You use the term ventricular premature **complex** (not *contraction*) in the body of the text?
- Line 43: European **Society for Veterinary Cardiology** - please use upper case for this title
- Line 53: Please **replace** "VPC" *with* "VPCs"
- Line 57: Please **replace** "guidelines provide also" *with* "guidelines also provide"
- Line 59: Please **replace** "but may" *with* "but **which** may"
- Line 69: Please **replace** "such as Doberman" *with* "such as **the** Doberman"
- Line 72: Please **replace** "Doberman Pinscher" *with* "Doberman Pinschers"
- Line 80: Please **replace** "was a disorder of primarily the" *with* "was **primarily** a disorder of the"
- Line 90: Please **replace** "slower" *with* "more slowly"
- Line 91: Please **insert** "ECG" *after* "(Holter)"
- Line 99: Please **replace** "and use both" *with* "and **to** use both"
- Line 100: Please **replace** "Given the disease" *with* "Given **that** the disease"
- Line 130: Please **replace** "reading" *with* "recording"
- Line 133: Please **replace** "software is notoriously inaccurate, manual adjustments" *with* "software **are** notoriously inaccurate **and** manual adjustments"
- Line 144: Please **replace** "as cut-off" *with* "as **the** cut-off"
- Line 145: Please **replace** "DCM, the authors" *with* "DCM, **but** the authors"
- Line 154: Please **replace** "diagnostic criterion" *with* "**a** diagnostic criterion"
- Line 156: Please **replace** "less likely caused" *with* "less likely **to be** caused"
- Line 160: Please **replace** "12 months will" *with* "12 months **with**"
- Line 180: Please **replace** "or a systolic" *with* "or systolic"
- Line 191: Please **replace** "hypothyroid group, and progressive" *with* "hypothyroid group. Progressive"
- Line 197: Please **replace** "The SMOD is" *with* "SMOD is"
- Line 198: Please **replace** "The SMOD" *with* "The left ventricular volume determined by SMOD"
- Line 200: Please **replace** "should not visible" *with* "should not **be** visible"
- Line 202: Please **replace** "selected in the" *with* "selected **from** the"
- Lines 210-211: Please **replace** "reduce estimations in" *with* "reduced estimations **of**"
- Line 229: Please **replace** "long axis were" *with* "long axis **view** were"
- Line 234: Please **replace** "from right parasternal" *with* "from **the** right parasternal"
- Line 241: Please **replace** "at nadir" *with* "at **the** nadir"
- Line 245: Please **replace** "dogs that are difficult to achieve" *with* "dogs where it is difficult to achieve"
- Line 248: Please **replace** "and is preferred" *with* "and **this** is preferred"
- Line 249: Please **replace** "current" *with* "**concurrent**"
- Line 254: Please **replace** "criteria" *with* "**criterion**"
- Line 263: Please **replace** "used" *with* "**using**"
- Line 267: Please **replace** "obtained from right" *with* "obtained from **the** right"
- Line 303: Please **replace** "6,5" *with* "6.5"
- Line 305: Please **replace** "Simpson" *with* "SMOD"
- Lines 313 **and** 695: Please **replace** "fore shortening" *with* "foreshortening"
- Line 333: Please **replace** "Biomarker" *with* "Biomarkers"
- Line 334: Please **replace** "normal, but at" *with* "Normal. But at"

- Line 343: Please **delete** “stages”
- Line 344: Please **replace** “Study” with “study”
- Lines 345 **and** 346: Please **replace** “Doberman” with “Dobermans”
- Line 352: Please **replace** “90.4%) reduction” with “90.4%. Reduction”
- Line 360: Please **replace** “only had” with “had only”
- Line 366: Please **replace** “lab” with “laboratory”
- Line 368: Please **replace** “to 1st” with “to **the** 1st”
- Line 381: Please **replace** “group. Suggesting” with “group, suggesting”
- Line 383: Please **delete** “the current gold standard”, as this is repetitive here?
- Line 391: Please **replace** “years of using” with “years using”
- Line 401: Please **replace** “azotemia” with “renal dysfunction”, as azotemia is a laboratory finding, not a “disease process”?
- Line 411: Please **replace** “and is” with “and it is”
- Line 415: Please **replace** “This study was also reported, that” with “This study also reported that”
- Line 420: Please **replace** “and is therefore as for NT-proBNP is” with “and therefore, as for NT-proBNP, it is”
- Lines 430-431: Please **replace** “realize, that not cTnI can be increased not only in dogs with DCM” with “realize that cTnI is not only increased in dogs with DCM”
- Lines 433-434: Please **replace** “Therefore, as systemic diseases should be excluded, if increased” with “Therefore systemic diseases should be excluded if increased”
- Line 449: Please **replace** “goal” with “gold”
- Line 454: Please **replace** “a gallop rhythm” with “an audible gallop sound”
- Line 456: Please **replace** “Doberman” with “Dobermans”
- Line 477: Please **replace** “outline” with “outlined”
- Line 481: Please **replace** “genic” with “genetic”
- Line 518: Please add the full name of the second author (Horne, R.)
- Line 567-569: Reference [20] is the same as reference [6]? - please delete [20] and renumber subsequent citations.
- Line 597: Please add the full citation information for Reference [28]

European Society of Veterinary Cardiology (ESVC) Screening Guidelines  
for Dilated Cardiomyopathy in Doberman Pinschers

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Running title: ESVC DCM Screening Guidelines Doberman

Keywords: DCM, cTNI, NT-proBNP, Simpson’s method of discs, 24-hours-ECG

Conflict of Interest: none related to this article

Abbreviation Table:

cTnI	cardiac troponin I
DCM	dilated cardiomyopathy
Doberman(s)	Doberman Pinscher(s)
ECG	resting electrocardiogram
EDV	end-diastolic volume
EPSS	E-point to septal separation
ESV	end-systolic volume
Holter	24-hour ambulatory electrocardiogram
LV	left ventricle
LVIDd	left ventricular internal diameter by M-Mode in diastole
LVIDs	left ventricular internal diameter by M-Mode in systole
NT-proBNP	N-terminal pro B-type natriuretic peptide
SI	sphericity index
SMOD	Simpson’s method of discs
VPC(s)	ventricular premature complex(es)

## **Abstract**

**Background:** Dilated cardiomyopathy (DCM) is the most common cardiac disease in large breed dogs and is inherited in Doberman Pinschers (Dobermans) with a high prevalence (58%).

**Objective:** The European Society for Veterinary Cardiology (ESVC) convened a task force to formulate screening guidelines for DCM in Dobermans.

**Recommendations:** Screening for occult DCM in Dobermans should start at three years of age and use both Holter monitoring and echocardiography. Yearly screening over the life of the dog is recommended, as a one-time screening is not sufficient to rule out future development of DCM. The preferred echocardiographic method is the measurement of the left ventricular volume by Simpson's method of discs (SMOD). Less than 50 single ventricular premature complexes (VPCs) in 24 hours are considered to be normal in Dobermans, although detection of any number of VPCs is cause for concern. Greater than 300 VPCs in 24 hours, or two subsequent recordings within a year showing between 50 to 300 VPCs in 24 hours is considered diagnostic of occult DCM in Dobermans regardless of the concurrent echocardiographic findings. The guidelines also provide recommendations concerning ancillary tests, that are not included in the standard screening protocol, but which may have some utility when recommended tests are not available or financially untenable on an annual basis. These tests include assay of cardiac biomarkers (Troponin I and N-Terminal pro-B type Natriuretic Peptide) as well as a 5-minute resting electrocardiogram (ECG).

**Conclusion:** The current guidelines should help to establish an early diagnosis of DCM in Dobermans.

## Introduction

Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilation.[1] Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular dilation and contractile dysfunction, in the absence of abnormal loading conditions and severe coronary artery disease.[2] Dilated cardiomyopathy is one of the most common cardiac diseases in dogs and humans.[1, 3] In the dog, it primarily affects large and giant breeds.[3] Some breeds, such as the Doberman, Newfoundland, Portuguese Water dog, Great Dane, Cocker Spaniel, and Irish Wolfhound exhibit a higher prevalence of DCM.[3-6]

**DCM** in Dobermans is an inherited, slowly progressive disease.[7-9] The occult stage of the disease is characterized by evidence of morphologic or electrical derangement in the absence of clinical signs of heart disease.[10-14] The occult stage may last for several years, before clinical signs develop.[8, 12] The morphologic abnormality consists of left ventricular (LV) enlargement in systole and later in diastole.[15] Ventricular premature complexes are a common finding in the occult stage of DCM in Dobermans.[6, 9, 10, 12-14, 16-20] Sudden death, caused by ventricular tachycardia-fibrillation, occurs during the occult stage in at least 25 to 30% of affected dogs.[6, 9, 17] These abnormalities, morphologic or electrical, may coexist or may be of predominantly one form at any time during the occult stage.[6, 10, 17, 21, 22]

A recent study showed a high cumulative prevalence (58.8%) of cardiomyopathy in Dobermans in Europe [8], comparable to that reported in the United States and Canada (45 and 63 %).<sup>a</sup>[21, 23]. The early descriptions of DCM in Dobermans suggested that cardiomyopathy predominantly affected males [13], and was later confirmed, although females are also affected.<sup>a</sup>[11-13, 17, 21] One study showed that in Dobermans, approximately 50% of male dogs and 33% of female dogs develop DCM<sup>a</sup>, whereas another study found no gender difference.[24] The most recent study showed that the disease is equally distributed in

male and female dogs in Europe.[8] The difference in reported gender distributions between earlier and later studies might be explained by the inconsistent inclusion of a 24-hour electrocardiogram (Holter) or ECG as part of the standard diagnostic screening in earlier studies. This could explain the over-representation of dogs with morphological changes of the heart, detectable by echocardiography. Generally, male dogs are known to show structural changes earlier than female dogs, which are detectable with an echocardiogram. Males are therefore more likely to develop CHF at an earlier age than female dogs, and likewise succumb from it earlier.[8] Female dogs seem to have a more slowly progressive disease with VPCs detected with a Holter as the only abnormality, even in older female dogs. However, most female Dobermans will develop the typical echocardiographically evident morphologic heart changes associated with DCM at an older age, compared with male dogs.[8] The average age of detection of occult DCM is between 5-7 years, but some dogs are affected as young as 2 years of age. Therefore, it appears appropriate to start screening for occult DCM in Dobermans at three years of age and to use both Holter monitoring and echocardiography. Given that the disease can develop over time in combination with the known rate of progression over several years, screening should ideally be repeated on an annual basis.[8, 12] In high-risk breeds, such as the Doberman, yearly screening over the life of the dog is recommended but can be cost prohibitive and requires a devoted owner. However, early detection of occult DCM can facilitate timely removal of affected dogs from active breeding programs and early treatment for all affected dogs leading to an increase in symptom free and overall survival.[22, 25] Removal of affected dogs from breeding programs should over time reduce the prevalence of DCM in Dobermans.

## **Recommendations**

### **Screening Age**

Screening should be started at 3 to 4 years of age. A one-time screening is not sufficient to rule out future development of DCM, because the disease is acquired and may develop with increasing age.

**Screening Frequency**

Yearly screening should be performed ideally in both male and female dogs. However, given male dogs involved in active breeding programs have the potential to pass on the disease to a greater number of progeny than female dogs if they are affected and not diagnosed, emphasis should be on annual screening of male dogs that are involved in active breeding programs. Female dogs involved in breeding programs, pets and non-breeding dogs could be screened once every 2 years if budgetary restrictions prevent annual screening.

**Holter Criteria**

It is essential that the Holter recording be of sufficient duration (at least 23 hours of readable recording), good quality and have an accurate analysis verified by a cardiologist. Holter reports generated by automated Holter analysis software are notoriously inaccurate and manual adjustments are always necessary. Inaccurate Holter reports can lead to both false positive and false negative results both of which can have a significant negative impact on breeders and pet owners.

Fewer than 50 single VPCs in 24 hours is considered to be normal in Dobermans, although detection of any number of VPCs is cause for concern.[6] Greater than 300 VPCs in 24 hours, or two subsequent recordings within a year showing between 50 to 300 VPCs in 24 hours is considered diagnostic of occult DCM in Dobermans regardless of the concurrent echocardiographic findings.[26] Many studies have used > 100 VPCs in 24 hours as the cut-off value for establishing a diagnosis of DCM, but the authors believe the results of the most recent study [26] should be the basis of current recommendations.

Comments on special situations:



- 1.) Holter examination shows 1 - 50 VPCs/24-hrs: In Dobermans, detection of any number of VPCs is cause for concern, even if only a few VPCs are detected in 24 hours (< 50 VPC/24-hrs). In these cases, VPCs that have a short coupling interval (maximum velocity of beat to beat coupling interval > 250/min) and complexity should also be considered as an additional diagnostic criterion, as couplets, triplets or single short runs of VPCs with a fast instantaneous rate (>260/min) are potentially dangerous and are less likely to be caused by myocardial damage secondary to other systemic diseases. In these cases DCM cannot be ruled out and a follow-up Holter examination should be performed within 3-6 months.
- 2.) Holters showing between 50 - 300 VPCs in 24 hours and a follow-up Holter within 12 months with < 50 VPCs. Dogs in this category remain a challenge as DCM cannot be definitively ruled out. In these cases ongoing screening is strongly recommended.
- 3.) It is also important to acknowledge, that some dogs will have normal echocardiograms but still have occult DCM diagnosed based on the Holter results. Systemic diseases that could potentially cause VPCs should always be excluded. Ventricular escape complexes and accelerated idioventricular rhythms (ventricular rate < 160 bpm) are not considered to be diagnostic for DCM. The role of atrial premature contractions and atrial tachycardia (excluding atrial fibrillation) in the diagnosis of DCM in Dobermans is currently unknown.
- 4.) The day-to-day variability of VPCs in Dobermans is currently unknown. In Boxer dogs and humans an individual day-to-day variability of up to 85% was reported.[27, 28]

### **Echocardiographic Criteria**

In general, the accuracy of the echocardiographic results will depend on the quality of the examination. A complete echocardiogram including color Doppler with a simultaneous ECG should be performed. Basic guidelines should be followed including all measurements being made in triplicate for

volume and 5 sequential (if possible) cardiac cycles for M-Mode.[29-31] Congenital or acquired cardiac diseases other than DCM might also cause volume overload, systolic dysfunction or both, and need to be excluded accordingly. Examples are patent ductus arteriosus, ventricular septal defect, mitral valve dysplasia or myxomatous mitral valve degeneration. Auscultation and color/spectral Doppler examinations should be used to exclude these and other diseases. Hypothyroidism [32-34] and DCM [8, 35] are both common diseases in the Doberman. Recently, it was shown that Dobermans with DCM have a 2.26 fold increased risk to develop hypothyroidism.[35] However, hypothyroidism does not seem to play a role in the etiology or progression of DCM in this breed. In this study, hypothyroid dogs were receiving optimal thyroid supplementation and there was no difference in cardiac size or number of VPCs between the healthy and hypothyroid group. Progressive increase in cardiac volume by SMOD and the number of VPCs was not different between the groups.[35]

## **Echocardiographic Measurements**

### Left ventricular volume by Simpson's Method of Discs:

Simpson's method of discs is more sensitive than M-Mode to detect early echocardiographic changes in Dobermans.[15] The left ventricular volume determined by SMOD should be measured in the right parasternal long axis 4-chamber view and in the left apical 4-chamber view (the aorta should not be visible in either view) by tracing the endocardial border on each selected image. The frame used to measure the End Diastolic Volume (EDV) is selected from the frames around the onset of the QRS-complex, when the mitral valve is closed and the volume at its largest (which may not be exactly at onset of the QRS complex) and the frame used to measure the End Systolic Volume (ESV) is selected as the last frame before mitral valve opening, typically after the end of the T wave, where the volume is at its smallest (Figure 1). Both right parasternal and left apical views should be measured and the larger volumes used, as this reduces potential underestimation of the volume. The tendency for apical foreshortening can easily lead to under-estimation of both ESV and EDV.

Cut-off values that indicate the presence of occult DCM based on left ventricular volume estimates by SMOD are [15]:

EDV Index (EDVI)=  $EDV(ml) / BSA(m^2)$ :  $> 95ml/m^2$

**or**

ESV Index (ESVI)= $ESV(ml) / BSA(m^2)$ :  $> 55 ml/m^2$

Body surface area (BSA) can be calculated from body weight (kg) using this formula[36]:

$BSA = 10.1 \times kg^{2/3} \times 100$

#### Left Ventricular M-mode Measurements:

As M-mode is still commonly measured, the authors recommend use of the following reference values if volume measurements by SMOD are not available. However, if M-mode values are normal, but the volume index(s) is/are enlarged, the authors recommend that the results should be based on the volume index estimates, as they are more sensitive than M-mode.

M-mode reference values using the right parasternal long axis view were obtained slightly differently in some studies.[22, 37] Whereas the reference values from Wess et al.[37] were obtained from a right parasternal long-axis four-chamber view, excluding the aorta (the same view as used for the SMOD measurements), the reference values from O'Grady[22] were obtained from the right parasternal long-axis inflow/outflow view, with the aorta visible in the image (Figure 2a and 2b). Others routinely use the right parasternal short-axis view at the level of the chordae tendinae to obtain M-modes of the left ventricle (Figure 3), ensuring the M-mode cursor bisects the left ventricular cavity. For all M-mode measurements, the left ventricular internal dimension in diastole (LVIDd) is obtained ideally at the onset of the QRS and in the absence of an ECG, the largest left ventricular internal dimension is selected. The left ventricular internal dimension in systole (LVIDs) is chosen at the nadir corresponding to the peak downward motion of the interventricular

septum along a single cursor, typically near the end of the T wave. Care should be taken to minimize poor cursor alignment as this often leads to overestimation of LVIDs. In dogs where it is difficult to achieve optimum alignment, a common complaint in Dobermans, and for which volume estimation is not possible, LVIDd and LVIDs can be acquired from 2 dimensional images and this is preferred over a poor M-mode image. Although concurrent measurements from all views are most likely similar, there is currently no study available comparing all 3 methods. However, O'Grady adapted his long-axis derived M-mode reference range for LVIDs for the short axis method and the short-axis cut-off value for LVIDs was used in the Protect study as an inclusion criterion. Therefore, when using M-mode reference values generated by different studies, the studies reported measurement method should ideally be used. One study did compare the accuracy of diagnosis of occult DCM in Dobermans using M-mode measurements and volume as estimated by SMOD and reported that SMOD (sensitivity 100 %, specificity 99%) was superior to M-mode using both O'Grady's (sensitivity 89%, specificity 99%) and Wess's reported M-mode reference ranges (sensitivity 90%, specificity 89%). [37] Both M-Mode measurements in that study were obtained from the right parasternal long axis using the right parasternal long-axis four-chamber view, excluding the aorta.

Cut-off values that indicate the presence of occult DCM based on M-mode as described by Wess [37] (obtained from the right parasternal long axis 4-chamber view, Figure 2A):

LVIDd (male any weight) > 48 mm

LVIDd (female any weight) > 46 mm

or

LVIDs (male and female any weight) > 36 mm

Comment: Although the diagnosis of DCM can be established if only one variable is above the reference values, the accuracy of diagnosis

improves if both, diastolic and systolic measurements, are above the cut-off values.

Cut-off values that indicate the presence of occult DCM based on M-mode as described by O'Grady [22] (right parasternal long axis M-mode using the inflow/outflow view, Figure 2B):

$LVIDd > 0.1749 \times \text{body weight (kg)} + 40.3 \text{ mm}$  and / or

$LVIDs > 0.1402 \times \text{body weight (kg)} + 26.7 \text{ mm}$

Cut-off values that indicate the presence of occult DCM based on M-mode as described by O'Grady and adapted for short axis [25] (right parasternal short axis M-mode or 2 dimensional, Figure 2C):

$LVIDs \geq 0.1402 \times \text{body weight (kg)} + 35.3 \text{ mm}$

### **Other secondary echocardiographic measures of systolic left ventricular function**

#### E-point to septal separation (EPSS)

E-point to septal separation measurement is obtained from the right parasternal long axis view or short axis view at the level of the tip of the septal mitral valve leaflet. E-point to septal separation is the distance of the maximal early diastolic motion (E-point) of the septal mitral valve leaflet to the interventricular septum (Figure 3). A recent study evaluated EPSS in the role of detecting occult DCM in Dobermans and showed that  $EPSS > 6.5\text{mm}$  is a valuable additional variable for the diagnosis of DCM, which when added to M-mode measurements can improve sensitivity and specificity to levels that are similar to volume estimates by SMOD.[38]

#### Sphericity index (SI)

The geometrical shape, i.e. the sphericity of the LV can be assessed by comparing left ventricular length in diastole obtained from a right

parasternal long axis or left parasternal apical four-chamber view (obtained at end diastole as per the SMOD with caution to avoid apical foreshortening) (Figure 4) to the M-mode LVIDd. The SI is calculated by dividing the length of the LV in diastole by the width of the LV in diastole. An SI <1.65 is associated with an increased sphericity and is considered abnormal according to the **ESVC** guidelines.[39] A study in Dobermans reported, that an SI < 1.65 is also the best cut-off to identify occult DCM in Dobermans. However, because the sensitivity and specificity of SI alone was not very good (sensitivity 86.8 %, specificity 87.6%) when compared to volume estimates using SMOD and EPSS, its inclusion as a recommended parameter in screening protocols for Dobermans is not warranted.[38]

#### **Ancillary tests, currently not included as standard screening tests:**

The following tests are currently not recommended for screening purposes, but may have some utility when recommended tests such as echocardiography and a Holter are not available or financially untenable on an annual basis.

Biomarkers such as cardiac troponin I (cTnI) [40] or N-Terminal pro B-type natriuretic peptide (NTproBNP) [41, 42] might be abnormal in some dogs, in which Holter and echocardiography are still normal. But at this time, there is not sufficient evidence that they can replace Holter and or echocardiography, but they might be valuable additional tests. N-Terminal pro B-type natriuretic peptide values > 500 pmol/L can predict echocardiographic changes consistent with occult DCM and the corollary is also true in that Dobermans with an NT-proBNP < 500 pmol/L are unlikely to have contemporaneous echocardiographic evidence of occult DCM.

#### **N-Terminal pro B-type natriuretic peptide (NT-proBNP)**

367 Screening for occult disease is one of the most promising areas of blood  
368 sample-based biomarker research. In one study including 328  
369 Dobermans, plasma NT-proBNP concentration was significantly higher in  
370 Dobermans with DCM, including those with occult DCM, diagnosed by  
371 echocardiography alone or both echocardiography and a Holter, than in  
372 healthy dogs.[41] The NT-proBNP assay was not clinically useful to detect  
373 disease in dogs presenting only with ventricular arrhythmias. In this study  
374 the best cut-off value for the prediction of echocardiographic  
375 abnormalities indicative of DCM was > 550 pmol/L (sensitivity 78.6%,  
376 specificity 90.4%). Reduction of the cutoff value to > 400 pmol/L  
377 increased the sensitivity to 90.0%, while specificity decreased to 75.0%.  
378 In a second study, the combined use of an NT-proBNP cutoff value > 457  
379 pmol/L and a Holter recording led to detection of occult DCM with a  
380 sensitivity of 94.5%, specificity of 87.8%, and overall accuracy of  
381 91.0%.[42] Similar to the aforementioned study [41], NT-proBNP  
382 concentration was most accurate for detection of occult DCM when  
383 Dobermans had echocardiographic changes indicative of occult DCM, but  
384 had poor accuracy for identification of dogs that had only ventricular  
385 arrhythmias. Both of these studies were performed using the 1st  
386 generation assay without use of the protease inhibitor tubes for sample  
387 collection (but immediately frozen at -80 C and then sent frozen for batch  
388 analysis). N-Terminal pro B-type natriuretic peptide values degrade over  
389 time, if the samples are not frozen and shipped cooled. This is especially  
390 important if the 1st generation assay is used. One laboratory is offering  
391 now a second-generation assay, which does not require protease inhibitor  
392 tubes and can be posted unfrozen. As this assay was designed to give  
393 similar results to the 1st generation assay, and was utilized in one study  
394 (abstract ECVIM) of 449 Dobermans screened with a combination of  
395 echocardiography and a 3-minute ECG.<sup>b</sup> This study reported that a cutoff  
396 of > 548 pmol/L had a sensitivity of 100% and a specificity of 80% to  
397 detect the characteristic echocardiographic morphologic changes of DCM  
398 with or without concurrent evidence of VPCs on a 3-minute ECG. These  
399 findings are not significantly different from those reported on earlier

generations of this assay and together emphasize the role of NT-proBNP testing in the Doberman.<sup>b</sup>

Despite its reported usefulness, the NT-proBNP assay does not replace recommended gold standard diagnostic procedures such as echocardiographic examination, for which the sensitivity and specificity of detecting left ventricular dysfunction can be as high as 97%.[15]

One study reported a longitudinal design that included follow-up examinations allowing the retrospective identification of a group of dogs (last-normal) that were determined to be normal according to gold-standard diagnostic methods (echocardiogram and Holter) at the time of NT-proBNP sample collection, but went on to develop DCM within 1.5 years of this evaluation.[41] Plasma NT-proBNP concentrations were significantly increased in this group, compared with concentrations in the control group, suggesting that DCM was detected in this group by NT-proBNP measurement earlier than was possible with a combination of echocardiography and a 24 hour Holter.[41] Validation of these results in other studies would be needed to make screening recommendations solely on blood based testing.

## **NT-proBNP Recommendations**

**NT-proBNP** appears to be especially useful to predict echocardiographic changes in Dobermans and it might be reasonable to screen dogs > 3 – 4 years using the NT-proBNP test. This type of testing could be considered when the owner cannot afford the expense of echocardiography and Holter recording. There is not sufficient evidence to support NT-proBNP testing alone in screening Dobermans when the other established tests are available and affordable. In addition, it cannot be used alone to establish a diagnosis on which to base a recommendation to begin therapy.[43]

As with any diagnostic test, certain limitations and considerations must be recognized when using the NT-proBNP assay. Circulating NT-proBNP concentration can be affected by concurrent disease processes such as renal dysfunction, pulmonary hypertension, sepsis, or systemic



hypertension as well as incorrect blood sample handling or use of the assay in inappropriate patients. Lastly, if repeated sampling is done as part of a screening protocol normal day-to-day variation should be taken into account.[44]

### **Troponin I**

Circulating cardiac troponin I has been demonstrated to be a highly specific and sensitive marker for myocardial cellular damage in humans and animals. The primary value of cTnI as a cardiac biomarker in humans is to detect myocardial infarcts [45]. It is reported to be significantly elevated in Dobermans with DCM.[40] Dogs with more advanced stages of the disease had the highest concentrations of cTnI. It was not only elevated in Dobermans with echocardiographic changes, but also in dogs that had only VPCs. This study also reported that cTnI was elevated in a very early stage of the disease ("last normal group" or "incipient group" as discussed above). Dogs in the "last normal" or "incipient" group had significantly higher cTnI values compared to control dogs. The best cut-off for cTnI to predict DCM using the Immulite assay was > 0.22 ng/mL (sensitivity 79.5% and specificity 84.4%) and therefore, as for NT-proBNP, it is a valuable additional diagnostic test to screen for cardiomyopathy in Dobermans when the gold standard is not available. It likewise suffers from similar limitations as outlined previously for NT-proBNP.[40] However, there is not sufficient evidence to support that this test could replace conventional methods such as echocardiography and Holter examinations.[40] Lastly, cTnI concentrations have also been shown to have an additional value for risk assessment of sudden cardiac death in Dobermans with an enlarged heart, using a cut-off value of > 0.34 ng/mL.[46]

It is important to realize that cTnI may be increased in dogs with systemic conditions or myocarditis and the cardiomyocyte injury indicated by increased cTnI is not specific for DCM.[40, 47-53]. Therefore systemic diseases should be excluded if increased cTnI levels are detected. There are different cTnI assays available and the test results might not be completely comparable. Ultrasensitive tests may detect even earlier

changes compared with this study and may lead to lower cut-off values. This needs to be investigated in future studies. One study in Dobermans reported a cTnI cut-off off > 0.139 ng/mL (ADVIA Centaur CP® Ultra-TnI; lower limit of detection of 0.006 ng/mL) had a 100 sensitivity and 79% specificity to detect the characteristic echocardiographic morphologic changes of DCM with or without concurrent evidence of VPCs on a 3-minute ECG.<sup>b</sup>

### **In House-ECG**

An in-house ECG cannot be used to replace a Holter examination. However, > 1 VPC/5 minutes is highly suggestive that > 100 VPCs will be recorded in 24 hours if a Holter is performed.[54] Therefore, when Holter and/or echocardiography are not available, or an owner wants to first have other tests performed, in order to be more convinced that further examinations (Holter, echocardiography) are necessary a combination of the following tests should be performed. However, it should be emphasized that these tests are not validated as sole screening tests, do not represent the gold standard screening tests and cannot be used to establish a diagnosis with which to make recommendations to begin treatment.

### **Clinical examination:**

A systolic murmur over the left apex, an audible gallop sound on auscultation, weak pulse quality, an arrhythmia or pulse deficits are all suspicious findings in Dobermans and represent a strong indication to proceed with additional tests.

### **Biomarker:**

NTproBNP result > 500 pmol/L

cTnI > 0.22 ng/mL

ECG: 1 VPC/5 minutes (or more) or atrial fibrillation are considered abnormal

If any of the above tests are abnormal, a further work-up including Holter examination and echocardiography is strongly recommended.

### **Genetic tests for DCM in Dobermans**

The genetic test based on the 16-bp deletion in the canine pyruvate dehydrogenase lipoamide kinase isozyme 4 (PDK4) might be useful in the USA [55], but may not be useful in Europe, as one study showed no association between PDK4 and DCM in a European study [56].

The results of genetic tests should not be used in place of standard screening. The absence of a genetic mutation known to be associated with a heritable disease such as DCM in Dobermans does not ensure the dog will never go on to develop DCM. In addition, the identification of a genetic mutation does not guarantee the dog will go on to develop DCM, and should not be considered a death sentence, but should be followed up with screening as outlined above. It is also clear there may be important regional differences even within a single breed and single disease. The real value of identifying genetic markers associated with heritable diseases may be to take them into consideration when selecting breeding pairs. Identification of genetic markers of heritable diseases in dogs and cats remains an active area of investigation.

### **Conclusions:**

Yearly screening over the life of the dog is recommended, as a one-time screening is not sufficient to rule out future development of DCM.

Screening for occult DCM in Dobermans should start at three years of age and use both Holter monitoring and echocardiography. The preferred echocardiographic method is the measurement of the left ventricular volume by **Simpson's method of discs (SMOD)**. Greater than 300 VPCs in 24 hours, or two subsequent recordings within a year showing between 50 to 300 VPCs in 24 hours is considered diagnostic of occult DCM in Dobermans regardless of the concurrent echocardiographic findings.

Ancillary tests, including biomarkers (cTnI and NT-proBNP) as well as in-house ECG recordings could be helpful in situations where the standard recommended tests are not available.

### **Footnotes**

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## Figures

### Figure 1:

Left ventricular volume by Simpson's Method of Discs. The SMOD should be measured in the right parasternal long axis 4-chamber view and in the left apical 4-chamber view (the aorta should not be visible in either view) by tracing the endocardial border on each selected image. The End-Diastolic Volume (EDV) is selected around the onset of the QRS-complex, when the mitral valve is closed and the volume largest (which might not be exactly where the QRS complex starts. The End-Systolic Volume (ESV) is selected typically near the end of the T wave, where the volume is smallest. Both right parasternal and left apical views should be measured.

### Figure 2:

Different methods used to generate reference intervals for M-Mode:

**2a:** right parasternal long-axis four-chamber view, excluding the aorta (the same view as used for the SMOD measurements) , as used for the reference values from Wess et al.[37]

**2b:** right parasternal long-axis inflow/outflow view, with the aorta visible in the image, as used for the reference values from O'Grady [22]

**2c:** right parasternal short-axis view at the level of the chordae tendinae to obtain M-modes of the left ventricle.

### Figure 3:

**EPSS** measurement is obtained from the right parasternal long axis view or short axis view at the level of the tip of the septal mitral valve leaflet.

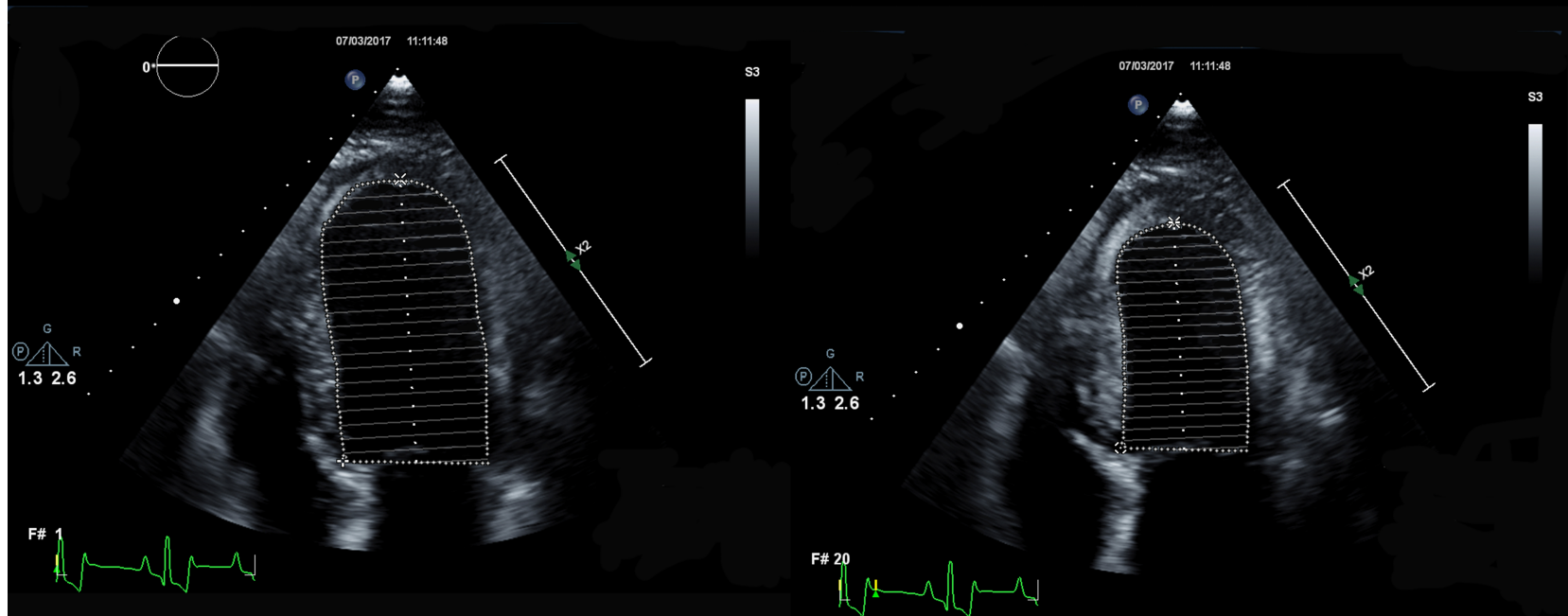
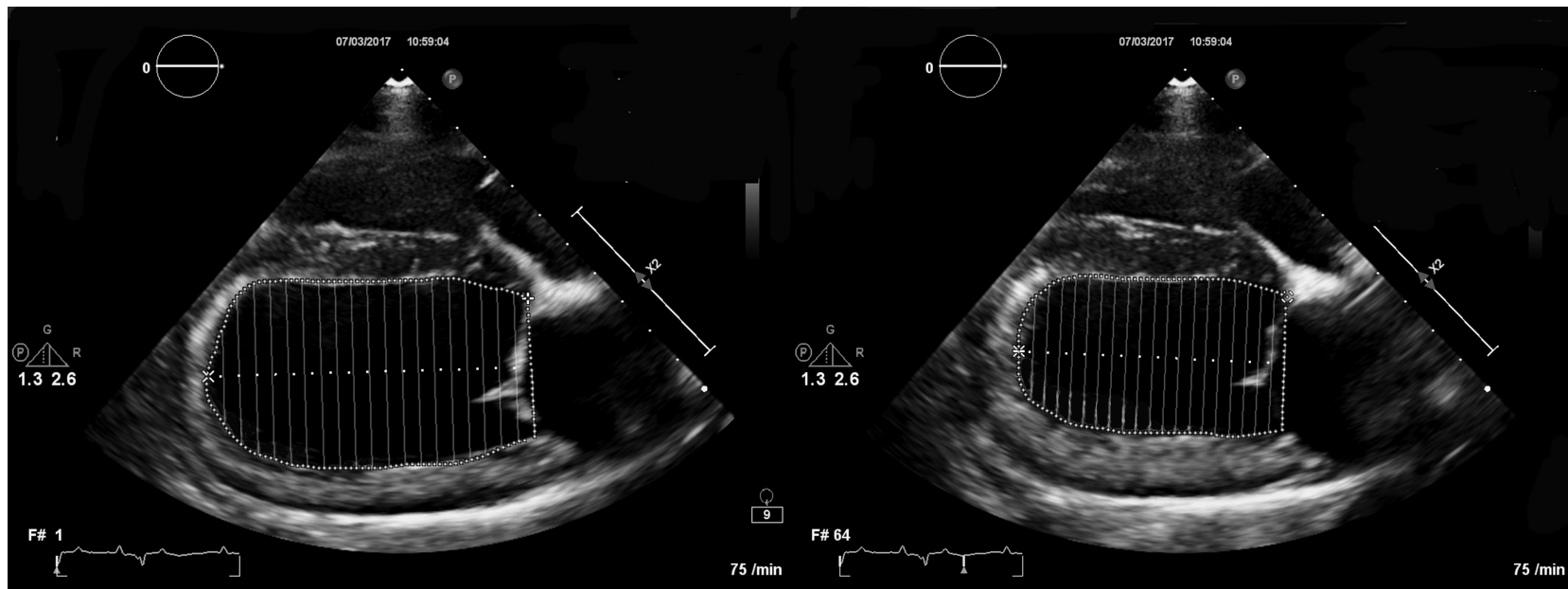
**EPSS** is the distance of the maximal motion (E-point) of the septal mitral valve leaflet to the interventricular septum during the rapid filling stage of diastole

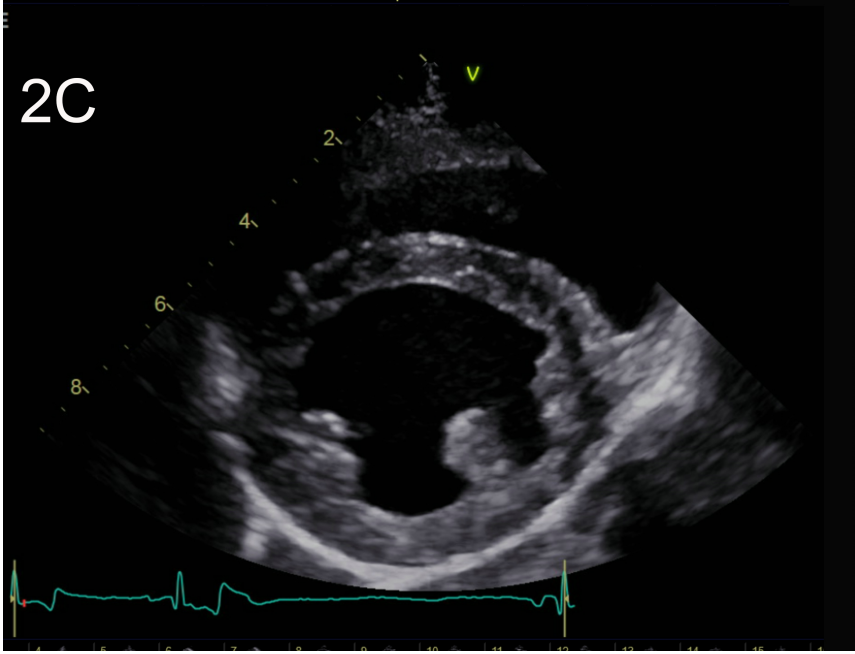
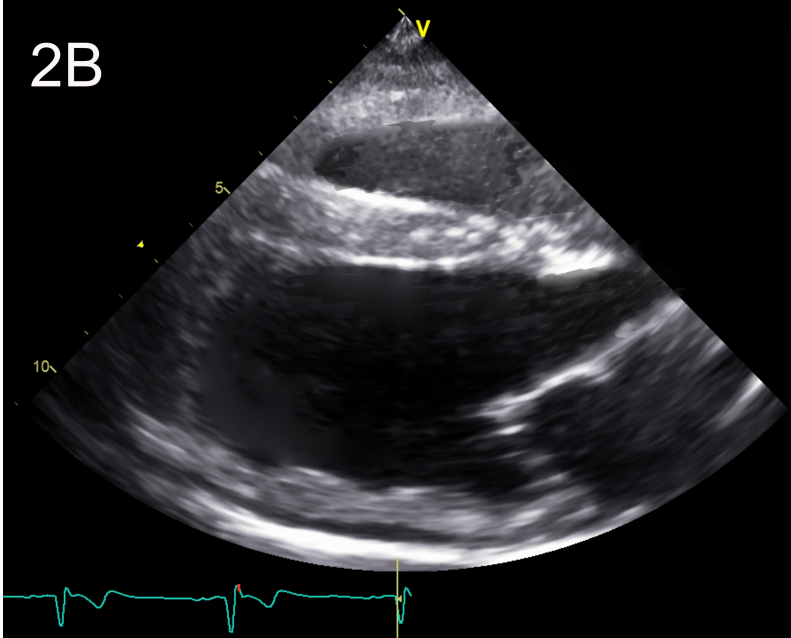
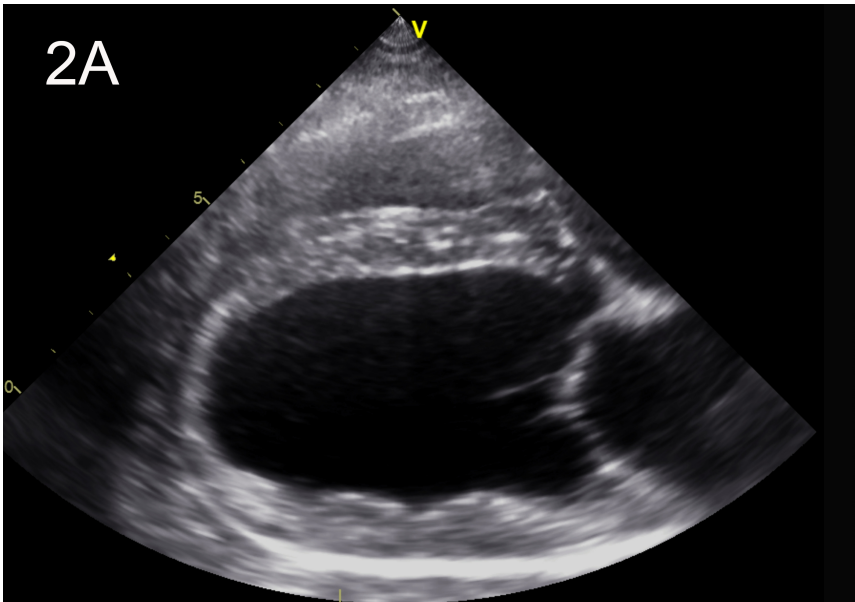
### Figure 4:

Sphericity index (SI)

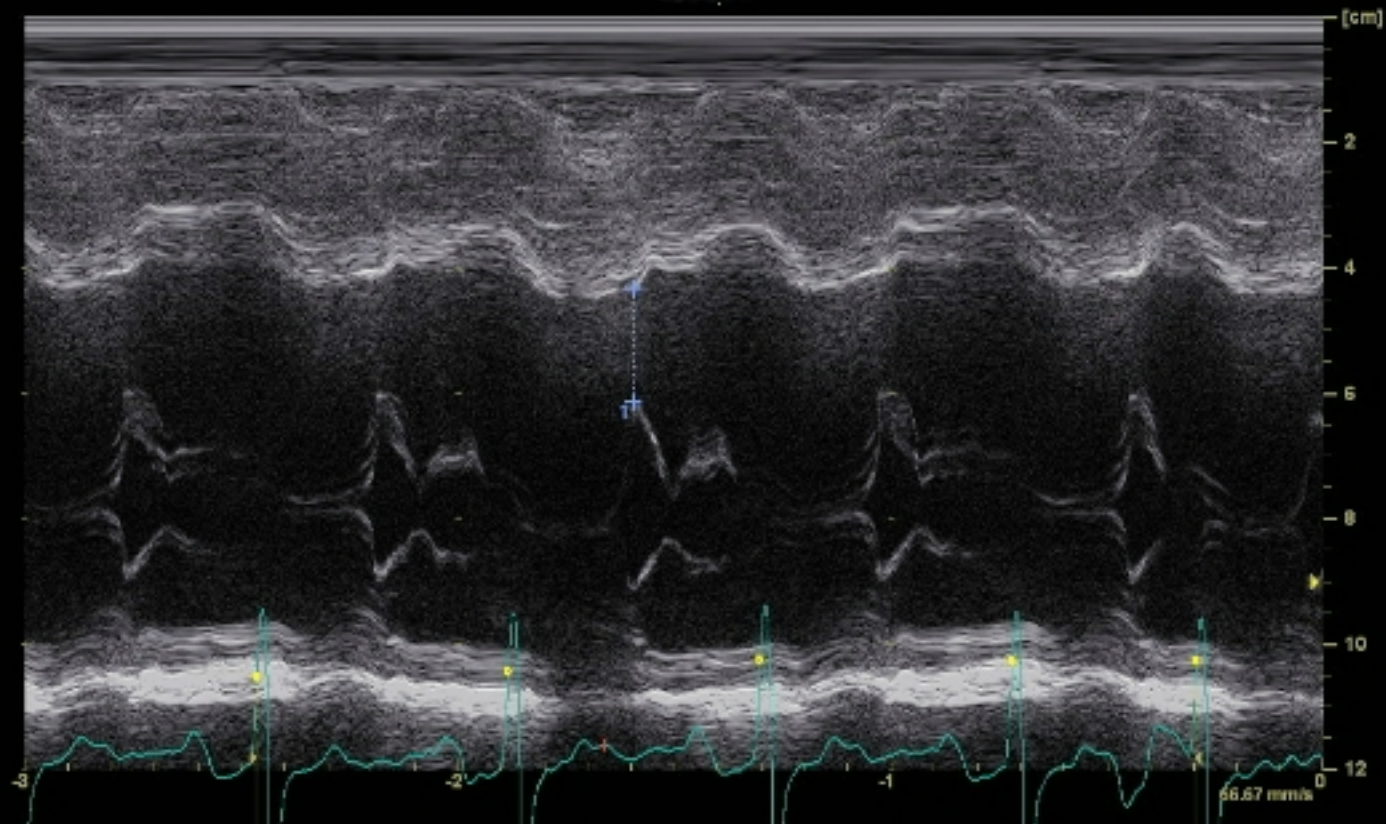
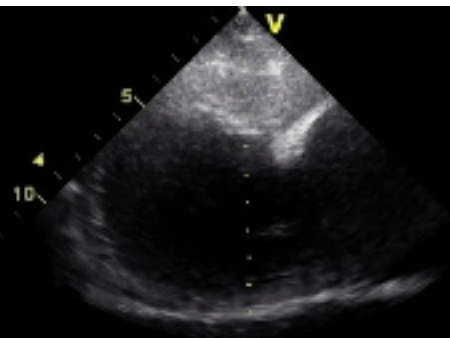
The geometrical shape, i.e. the sphericity of the left ventricle (LV) can be assessed by comparing left ventricular length in diastole obtained from a

791 right parasternal long axis or left parasternal apical four-chamber view  
792 (obtained at end diastole as per the SMOD with caution to avoid apical  
793 fore shortening) to the M-mode LVIDd. The SI is calculated by dividing the  
794 length of the LV in diastole by the width of the LV in diastole.





1 EPSS 18.06 mm



104  
HR



